

**ABSTRACT**

The instant invention provides stable and novel lineage I WNV reverse genetics systems, and methods for making the reverse genetics systems, specifically, a fully-infectious lineage I WNV cDNA or replicon system engineered with one or more nucleotide sequences each encoding a reporter gene to be used in high throughput cell-based screening assays for the identification of novel ant Flaviviral chemotherapeutics and/or vaccines effective to treat and/or immunize against infections by WNV and other emerging flaviviruses, such as, for example, JEV, SLEV, AV, KV, JV, CV, YV, TBEV, DENV-1, DENV-2, DENV-3, DENV-4, YFV and MVEV. The present invention further provides methods of high throughput screening of ant Flaviviral compounds or improved derivatives thereof using novel lineage I WNV reverse genetics systems and/or cell lines stably containing the reverse genetics systems. Also, the invention provides novel pharmaceutical compositions comprising an attenuated lineage I WNV that is less virulent but similarly immunogenic as the parent WNV and is capable of providing a protective immune response in a host.